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Science Advisory Board
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EPA

# AN SAB REPORT: REVIEW OF DRAFT PASSIVE SMOKING HEALTH EFFECTS DOCUMENT

## REVIEW, BY THE INDOOR AIR QUALITY AND TOTAL HUMAN EXPOSURE COMMITTEE, OF THE OFFICE OF RESEARCH AND DEVELOPMENT'S DRAFT REPORT: "RESPIRATORY HEALTH EFFECTS OF PASSIVE SMOKING: LUNG CANCER AND OTHER DISORDERS" (EPA/600/6-90/006B)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

November 20, 1992

OFFICE OF
THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

EPA-SAB-IAQC-93-003

Honorable William K. Reilly
Administrator
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Subject: Review of the Environmental Tobacco Smoke Risk Assessment - *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders* (EPA/600/6-90/006B)

Dear Mr. Reilly:

The Science Advisory Board's (SAB) Indoor Air and Total Human Exposure Committee (IAQTHEC) met on July 21-22, 1992 to review the draft EPA document *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders* (EPA/600/6-90/006B, May 1992 SAB Review Draft). This is the second review conducted by this committee on this issue; the first being conducted on December 4-5, 1990. The Committee reported its earlier findings to you in our April 1991 report, *An SAB Report: Review of Draft Environmental Tobacco Smoke Health Effects Document* (EPA-SAB-IAQC-91-007, April 1991). This second draft document is much revised and expanded from the first document we reviewed and, for the most part, reflects the advice presented in our April 1991 report. As a result of our recent public review, the Committee provided to the EPA Staff detailed editorial and substance comments on the draft document. The attached report contains the Committee's broad recommendations and its responses to fifteen specific questions.

The Committee is pleased to note the great improvement in the discussion and analysis of effects of environmental tobacco smoke (ETS) on the health of children. The coverage of the pertinent literature is much more complete, and the specification and quantitation of the identifiable health risks are presented in a clear and defensible manner. This new material provides a basis for the Agency to

issue an overall risk assessment on ETS that gives an appropriate emphasis to non-cancer health effects. We also note that the revised draft has an improved presentation, discussion, and analysis of ETS as a lung carcinogen, providing a firmer basis for the designation of ETS as an EPA Class A Carcinogen. The Committee was unanimous in endorsing this classification.

This second draft, as a whole, is a very substantially improved document and, in general, does a good job of presenting the scientific evidence that supports the judgment that exposure to ETS causes lung cancer and other adverse respiratory health effects. It presents the data and relevant analysis in greater detail than is available in any other single source. In general, the findings are well substantiated, although further improvements are recommended for the new Chapter 3. Other changes made from the first draft to the current draft were carefully thought out and generally appropriate. Also, the authors have done a commendable job in addressing the points raised by the Committee in its review of the first draft. This document will be an invaluable source of information for health professionals and policy makers for years to come.

We appreciate the opportunity to review this draft document and look forward to your response to our advice contained in the attached report.

Sincerely,

Raymond C. Loehr

Dr. Raymond C. Loehr, Chair
Science Advisory Board

Morton Lippmann

Dr. Morton Lippmann, Chair
Indoor Air Quality and Total
Human Exposure Committee

## ABSTRACT

The Science Advisory Board's (SAB) Indoor Air and Total Human Exposure Committee (IAQTHEC) met on July 21-22, 1992 to review the draft EPA document *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders* (EPA/600/6-90/006B, May 1992 SAB Review Draft). The Committee provided responses to fifteen specific questions and provided commentary on chapters of the draft document. The Committee noted the great improvement in the discussion and analysis of effects of environmental tobacco smoke (ETS) on the health of children. The coverage of the pertinent literature is much more complete in this draft than in the previous draft, and the specification and quantitation of the identifiable health risks is presented in a clear and defensible manner. This new material provides a basis for the Agency to issue an overall risk assessment on ETS that gives an appropriate emphasis to non-cancer health effects. The Committee also noted that the revised draft has an improved presentation, discussion, and analysis of ETS as a lung carcinogen, providing a firmer basis for the designation of ETS as an EPA Class A Carcinogen. The Committee was unanimous in endorsing this classification.



KEYWORDS: Environmental Tobacco Smoke; ETS; Carcinogenicity; Passive Smoking; Sidestream Smoke; Mainstream Smoke; Confounders; Lung Cancer; Respiratory Disease

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U.S. Environmental Protection Agency
Science Advisory Board
Indoor Air Quality and Total Human Exposure Committee

Environmental Tobacco Smoke Review

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# 1. EXECUTIVE SUMMARY

The Science Advisory Board's (SAB) Indoor Air and Total Human Exposure Committee (IAQTHEC) met on July 21-22, 1992 to review the draft EPA document *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders* (EPA/600/6-90/006B, May 1992 SAB Review Draft). This is the second review conducted by this committee on this issue; the first being conducted on December 4-5, 1990. The Committee reported its findings to the EPA Administrator in our April 1991 report, *An SAB Report: Review of Draft Environmental Tobacco Smoke Health Effects Document* (EPA-SAB-IAQC-91-007, April 1991). The Committee made a number of substantive as well as structural recommendations, most of which have been addressed in the present draft document.

The Committee is pleased to note the great improvement in the discussion and analysis of effects of environmental tobacco smoke (ETS) on the health of children. The coverage of the pertinent literature is much more complete, and the specification and quantitation of the identifiable health risks are presented in a clear and defensible manner. This new material provides a basis for the Agency to issue an overall risk assessment on ETS that gives an appropriate emphasis to non-cancer health effects. We also note that the revised draft has an improved presentation, discussion, and analysis of ETS as a lung carcinogen, providing a firmer basis for the designation of ETS as an EPA Class A Carcinogen. The Committee was unanimous in endorsing this classification.

As a result of the public review, the Committee provided to the EPA Staff detailed editorial and substance comments on the draft document. This report contains the Committee's broad recommendations and its responses to fifteen specific questions in several categories from the charge to the Committee:

<u>ETS Exposure</u>

a) Do the conclusions on the chemical similarities of ETS and mainstream smoke (MS) warrant the toxicological comparison between passive and active smoking made as part of the biological plausibility arguments for lung cancer (Chapter 4) and non-cancer respiratory disorders (Chapter 7)?

Yes. All of the major carcinogenic and toxic agents found in mainstream smoke are also present in ETS, albeit at lower concentrations. The combustion of tobacco to form sidestream smoke (SS) actually results in slightly higher amounts of many toxic and carcinogenic compounds per gram of tobacco burned than when the tobacco is burned to produce mainstream smoke. However, Chapter 3, as written, did not adequately make this case and requires some modification. The following issues should be addressed in Chapter 3 to support this similarity.

- Many of the same carcinogenic compounds are found in MS and SS and ETS (measured in smoky rooms), i.e., the polycyclic aromatic hydrocarbons, the N-nitrosamines, and 4-aminobiphenyl. Many of these compounds are substantially enriched in SS relative to MS by factors ranging from about 2 to 100, although overall exposure to ETS will be much lower than to MS. Thus, as a complex mixture, SS might be expected to be somewhat more potent as a carcinogenic mixture.

- Extracts of particulate matter from combustion mixtures have consistently been shown to be carcinogenic in animal bioassays, mutagenic in short-term *in vitro* bioassays, and carcinogenic in humans, although potencies can vary.

- Many of the individual organic compounds in MS, SS and ETS have also been found to be carcinogenic in animals, e.g., many of the polycyclic aromatic hydrocarbons, the N-nitrosamines and 4-aminobiphenyl.

b) Is the extent of ETS exposure in various environments adequately characterized?

Yes. ETS exposure has been characterized in several different ways, in many environments. ETS is virtually ubiquitous, and concentrations and other characteristics have been consistently demonstrated in a very large number of environments. It is unlikely that further quantitative and qualitative description would provide much critical additional or different insights that would impact on the overall conclusions of the risk assessment.

c) Are the methods of assessing ETS exposure and the uncertainties associated with each accurately described?

Yes. The methods, and the problems and limitations are well described. Given the caveats and uncertainties, the different methods produce results which are confirmatory of each other. The questionnaire method, which has the inherent problem of information bias, has been validated, and the misclassification has been estimated in several studies. The degree of misclassification is different in different studies, as one would expect with instruments and study protocols that are different.

Lung Cancer - Hazard Identification

d) Is the evidence for the lung carcinogenicity of ETS presented adequately?

Yes. The report has been strengthened by the addition of Chapter 4 which reviews toxicologic evidence and highlights the evidence on active smoking. The epidemiologic data are adequately described, although formal criteria should be set forth for assigning the studies to tiers.

e) Does any of the new information alter the SAB conclusion regarding the categorization of ETS as an EPA Group A carcinogen?

No. The conclusion that ETS should be categorized as a Group A carcinogen, made in the initial EPA draft, remains valid with the addition of the new information in the revised draft. Despite the uncertainty about the magnitude of the risk of lung cancer due to passive smoking, the overall evidence is sufficient to declare that prolonged exposure to ETS is etiologically related to lung cancer and that ETS should be regarded as an EPA Group A carcinogen.

Lung Cancer - Population Impact

f) Is the approach used to derive estimates of U.S. female never-smoker lung cancer risk scientifically defensible?

Yes. The combination of U.S. epidemiologic studies of non-smoking women married to smokers provides an appropriate and sound basis for estimating the

relative risk of lung cancer associated with ETS among American women who have never smoked cigarettes.

g) Is the approach used to extrapolate lung cancer risk from female never-smokers to male never-smokers and former smokers of both sexes scientifically defensible?

Yes. Although alternative approaches also might have merit, the approach of extrapolating lung cancer mortality rates among women to men, which was used in the draft document, is scientifically defensible. However, the uncertainties should be further acknowledged. On the other hand, we advise caution in extending the risk assessment to ex-smokers who are known to remain at increased risk of lung cancer well beyond 5 years following cessation of smoking.

h) Are the assumptions used to derive these lung cancer population estimates and the uncertainties involved characterized adequately?

Yes. While the overall point estimate of approximately 3,000 total lung cancer deaths (LCDs) due to ETS exposure annually in the United States is based on reasonable assumptions, the citation of a range of 2,500 to 3,300 ETS-related LCDs, based on varying only one of the parameters involved in the estimation, is misleading and implies a greater degree of precision in the estimation than is warranted. The document would be strengthened by additional acknowledgement and characterization of these uncertainties.

i) Is the degree of confidence in these estimates as stated appropriately characterized?

No. The confidence in these estimates, represented by the range of 2,500 to 3,300 deaths due to ETS, understates the uncertainties associated with each of the assumptions that went into the risk assessment. It indicates a much higher degree of precision than the 90% confidence interval surrounding the summary relative risk for spousal smoking in the U.S. of 1.19. There are other assumptions used in the risk assessment that increase the uncertainty.

j) Have the biological plausibility arguments been adequately presented?

Yes. Biological plausibility has been adequately presented, except for the importance of bronchial responsiveness, especially in relation to lung function growth and decline.

k) Have the most important confounders been properly addressed?

Yes, most of them have. Low birth weight is a confounder that is not adequately considered by many studies. Also, ETS exposure in childhood and adolescence should be included in assessing the effects of ETS on lung functions in adults.

l) Has the weight of evidence been properly characterized? Are the conclusions scientifically defensible?

Yes. The weight of evidence has been properly characterized for most sections in Chapter 7, but the evidence for adult pulmonary function does not take into account the potential confounders of childhood respiratory diseases or exposures to parental smoking. The weight of evidence for asthma and sudden infant death syndrome (SIDS) is properly characterized, concluding causality for increased episodes and exacerbation of symptoms in asthmatics, but insufficient evidence for causality for asthma induction or SIDS.

m) Is the evidence with respect to maternal smoking and sudden infant death syndrome properly characterized? Should this evidence be included in this report?

Yes. The evidence is appropriately characterized in terms of the strong association and the Centers for Disease Control (CDC, 1991) Risk Assessment. Given the existing data, one cannot determine whether this is an *in utero* effect or an effect of environmental smoke exposure.

Population Impact

n) Is the presented population impact of ETS on lower respiratory infections and asthma in children scientifically defensible?

Yes. The issues related to asthma are clearly based on current knowledge. The focus should be on the exacerbation of asthmatic attacks because the etiology of the disease is difficult to define. The issue of childhood respiratory illnesses carries significant weight in the conclusions. It could be expanded, especially for population impact above age 18 months. Potential impact of both asthma and respiratory illnesses on adult lung function and disease could be explored further. The presentation of both a threshold and a non-threshold analysis is balanced, and the levels ascribed are consistent.

o) Are the assumptions, uncertainties, and degree of confidence in the ranges of population impact estimates adequately characterized?

Yes, for the most part. There is a complete description of the assumptions and uncertainties in the dataset. This is an enormous improvement from the first draft of this document, and provides a solid scientifically defensible base upon which to draw the conclusions made by the document.

# 2. INTRODUCTION

## 2.1 Background

The Science Advisory Board's (SAB) Indoor Air and Total Human Exposure Committee (IAQTHEC) met in public session on July 21-22, 1992 in Arlington, Virginia to review the draft EPA document *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders* (EPA/600/6-90/006B, May 1992 SAB Review Draft). At this public meeting, the Committee received presentations from Agency staff concerning the draft document, and public comments from 15 individuals representing themselves or various groups with an interest in this matter, including the R.J. Reynolds Company, the Tobacco Institute, Action on Smoking and Health, the Coalition on Smoking OR Health, and the Centers for Disease Control. The Committee also received written comments from 27 individuals or groups. Since the Agency did not initiate a formal public comment period, the SAB was the sole recipient of formal public comments under the provisions of the Federal Advisory Committee Act. Copies of all written comments were provided to the Committee prior to the public meeting, as well as to Agency staff for their consideration in revising the draft document.

This constitutes the second review conducted by this committee on this issue. This draft document is a revision of an earlier EPA draft report formerly titled, *Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children*, which the Committee reviewed on December 4 and 5, 1990. Our earlier findings (*An SAB Report: Review of Draft Environmental Tobacco Smoke Health Effects Document*, EPA-SAB-IAQC-91-007, April 1991) concurred with EPA's conclusions that ETS should be designated a Group A or known human carcinogen, but suggested that the conclusions on respiratory disorders in children could be made stronger. Our report also suggested several areas in which the health risk assessment could be improved, and offered to provide additional advice on a revised document.

The draft document has been significantly revised from the 1990 draft, and is quite different in size as well as format. The current draft is about 600 pages in length, compared to the 350 of the earlier draft. The increased size is the result of several changes, including: a new Chapter (3) on physical/chemical components and assessing exposure to ETS; a new Chapter (4) on the relationship of active smoking

and lung cancer; an expanded Appendix (Appendix A), which includes a review of all the pertinent ETS lung cancer studies in non-smoking women; a rewrite of the noncancer respiratory disorders Chapter (7) to include approximately thirty more studies than did the 1990 draft; and a new quantitative risk assessment Chapter (8) on noncancer respiratory effects.

As a result of our earlier review, two appendices from the EPA initial draft were dropped in the revision. These dealt mostly with lung deposition modelling and active to passive smoking dose-response modelling. As we suggested in our earlier report, some of the material from these appendices was extracted and included in Chapters 3 and 4 of the revised draft.

## 2.2 Charge to the Committee

The Agency sought the advice of the SAB on the accuracy and completeness of the entire document and on whether the Agency has been responsive to the Committee's previous recommendations. In addition, the SAB was asked to address the following specific issues:

A - ETS EXPOSURE (Chapter 3)

a) Do the conclusions on the chemical similarities of ETS and MS warrant the toxicological comparison between passive and active smoking made as part of the biological plausibility arguments for lung cancer (Chapter 4) and non-cancer respiratory disorders (Chapter 7)?

b) Is the extent of ETS exposure in various environments adequately characterized?

c) Are the methods of assessing ETS exposure and the uncertainties associated with each accurately described?

B - LUNG CANCER

1. HAZARD IDENTIFICATION (Chapters 4 and 5)

   a) Is the evidence for the lung carcinogenicity of ETS presented adequately?

   b) Does any of the new information alter the SAB conclusion regarding the categorization of ETS as an EPA Group A carcinogen?

2. POPULATION IMPACT (Chapter 6)

   a) Is the approach used to derive estimates of U.S. female never-smoker lung cancer risk scientifically defensible?

   b) Is the approach used to extrapolate lung cancer risk from female never-smokers to male never-smokers and former smoker of both sexes scientifically defensible?

   c) Are the assumptions used to derive these lung cancer population estimates and the uncertainties involved characterized adequately?

   d) Is the degree of confidence in these estimates as stated appropriately characterized?

C - NON-CANCER RESPIRATORY DISORDERS

1. HAZARD IDENTIFICATION (Chapter 7; Sections 8.1 and 8.2)

   a) Have the biological plausibility arguments been adequately presented?

   b) Have the most important confounders been properly addressed?

c) Has the weight of evidence been properly characterized? Are the conclusions scientifically defensible?

d) Is the evidence with respect to maternal smoking and sudden infant death syndrome properly characterized? Should this evidence be included in this report?

2. POPULATION IMPACT (Chapter 8)

a) Is the presented population impact of ETS on lower respiratory infections and asthma in children scientifically defensible?

b) Are the assumptions, uncertainties, and degree of confidence in the ranges of population impact estimates adequately characterized?

## 2.3 Format of this report

Although a major focus of the Committee's review is the response to the questions in the charge, the Committee also provided detailed commentary on each chapter of the document, both in the meeting transcript and in written comments. This report consists of 4 major chapters. An Executive Summary, an Introduction, Responses to the Questions in the Charge, and Comments on the Draft Document. Detailed editorial comments were omitted.

## 3. RESPONSES TO THE QUESTIONS IN THE CHARGE

### 3.1 Questions Concerning ETS Exposure (Chapter 3)

a) Do the conclusions on the chemical similarities of ETS and mainstream smoke (MS) warrant the toxicological comparison between passive and active smoking made as part of the biological plausibility arguments for lung cancer (Chapter 4) and non-cancer respiratory disorders (Chapter 7)?

Yes, all of the major carcinogenic and toxic agents found in MS are also present in ETS, albeit at lower concentrations. The combustion of tobacco to form ETS actually results in slightly higher amounts of many toxic and carcinogenic compounds per gram of tobacco burned than when the tobacco is burned to produce mainstream smoke. There are substantial differences in the relative composition of the smoke formed between mainstream and sidestream smoke, similar to the differences between the MS formed by different currently manufactured cigarettes, but there is no reason to suppose that the qualitative toxicities of ETS and MS are substantively different. In comparing these two agents the differences are largely ones of dose and duration of exposure rather than fundamental differences in the toxicity or carcinogenicity of the agent in question. However, Chapter 3, as written, did not adequately make this case and requires some modification. The following issues should be addressed in Chapter 3 to support this similarity.

- Many of the same carcinogenic compounds are found in MS and SS and ETS (measured in smoky rooms), i.e., the polycyclic aromatic hydrocarbons, the N-nitrosamines, and 4-aminobiphenyl. Many of these compounds are substantially enriched in SS relative to MS by factors ranging from about 2 to 100, although overall exposure to ETS will be much lower than to MS. Thus, as a complex mixture, SS might be expected to be somewhat more potent as a carcinogenic mixture.

- Extracts of particulate matter from combustion mixtures have consistently been shown to be carcinogenic in animal bioassays, mutagenic in short-term *in vitro* bioassays, and carcinogenic in humans, although potencies can vary.

- Many of the individual organic compounds in MS, SS and ETS have also been found to be carcinogenic in animals, e.g., many of the polycyclic aromatic hydrocarbons, the N-nitrosamines and 4-aminobiphenyl.

b) Is the extent of ETS exposure in various environments adequately characterized?

Adequate is a relative word. ETS exposure has been characterized in several different ways, in many environments. ETS is virtually ubiquitous, and concentrations and other characteristics have been consistently demonstrated in a very large number of environments. It is unlikely that further quantitative and qualitative description would provide much critical additional or different insight that would impact on the overall conclusions of the risk assessment.

Precise calculation of the expected risk due to ETS exposure would require detailed estimates on a population base for all of the United States for various ETS exposures. This database does not exist. However, there is a vast array of data on samples of the population and samples of the environments that can be extrapolated to the U.S. general population with an acceptable degree of certainty. These measures include traditional atmospheric measures of constituents of the smoke as well as individual dosimetry from individual monitors and from samples of biologic fluids for constituents of tobacco smoke and/or metabolic products of such constituents. As the report describes, one would expect some variation in the U.S. population in the degree of exposure to these agents, and the report describes the process for taking into account this variability in calculating numbers of deaths that are presented in the document. The data on exposure to the population in question are adequate to make the risk assessments that have been made, and are substantially more complete than the exposure estimates that are available for many other Class A carcinogens.

c) Are the methods of assessing ETS exposure and the uncertainties associated with each accurately described?

The methods, and the problems and limitations are well described. Given the caveats and uncertainties, the different methods produce results which are confirmatory of each other. The questionnaire method, which has inherent problems of information bias, has been validated, and the misclassification has been

The evidence for the carcinogenicity of ETS is presented in several logical components: evidence for MS inhalation being causal for lung cancer in proportion to dose, evidence for the reduction in risk following cessation of smoking, animal evidence for the carcinogenicity of MS and ETS, and evidence of mutagenicity of MS end ETS components. Finally the results of a large number of epidemiological studies of ETS exposures in non-smoking and never-smoking populations, and the increase in lung cancer risk associated with such exposures, are presented in great detail. These community exposures are shared by a very large fraction of the population and, although the risks are small compared to the risks of active smoking, they are quite consistent. Any studies involving low relative risks are likely to be controversial: there always are methodological short-comings.

b) Does any of the new information alter the SAB conclusion regarding the categorization of ETS as an EPA Group A carcinogen?

The conclusion that ETS should be categorized as a Group A carcinogen, made in the initial EPA draft, remains valid with the addition of the new information in the revised draft. The totality of epidemiologic evidence indicates that non-smoking women married to smokers have experienced an increased risk of lung cancer. Increased risks have been observed in most of the investigations in various parts of the world, including the United States. Biomarker studies have shown that nonsmokers exposed to ETS inhale and metabolize compounds in cigarette smoke, leaving no doubt that some of the various classes of carcinogens in tobacco smoke reach bodily tissues. Although concentrations of tobacco smoke components are much lower in ETS than in mainstream cigarette smoke, ETS and MS share many qualitative chemical similarities and, for many carcinogens, the relative proportion in ETS is enriched. Because cigarette smoking is such a well-established risk factor for lung cancer, and one that exhibits no evidence for a threshold, it is biologically plausible that prolonged inhalation of ETS results in some increase in risk of lung cancer among nonsmokers. Thus, despite the uncertainty about the magnitude of the risk of lung cancer due to passive smoking, the overall evidence is sufficient to declare that prolonged exposure to ETS is etiologically related to lung cancer and that ETS should be regarded as an EPA Group A carcinogen.

estimated in several studies. The degree of misclassification is different in different studies, as one would expect with instruments and study protocols that are different.

Although several possible markers for ETS are mentioned, two, respirable suspended particulate matter (RSP) and nicotine, are discussed most fully. The major uncertainties related to RSP as a marker are that the other sources of RSP in all environments vary from environment to environment. At low smoking levels, the RSP attributable to ETS is difficult to determine directly, and estimates of ETS in these cases are unstable. By contrast, ETS is the only source of nicotine in most environments, so that even at low smoking levels nicotine can be quantified and attributed entirely to ETS. The major limitations of vapor phase nicotine are that it is deposited onto surfaces more quickly than other components of ETS and also is re-emitted from these surfaces. On the other hand, the successful use of these two markers in field studies argues that these uncertainties are relatively small. The wide range of ETS concentrations reported in human environments where smoking occurs--over two and up to three orders of magnitude--indicate that the current degree of uncertainty in assessing ETS exposures can be tolerated.

Of the possible biomarkers of ETS exposure, cotinine and nicotine in body fluids (saliva, blood, and urine) are discussed most extensively. The advantages and limitations of these are accurately described, except that there should be some discussion of the possible dietary sources of nicotine and cotinine, and the contribution these might make to measured levels of these compounds in nonsmokers.

## 3.2 Questions Concerning Lung Cancer - Hazard Identification (Chapters 4 and 5)

a) Is the evidence for the lung carcinogenicity of ETS presented adequately?

Yes, the report has been strengthened by the addition of Chapter 4 which reviews toxicologic evidence and highlights the evidence on active smoking. The epidemiologic data are adequately described, although formal criteria should be set forth for assigning the studies to tiers.

## 3.3 Questions Concerning Lung Cancer - Population Impact (Chapter 6)

a) Is the approach used to derive estimates of U.S. female never-smoker lung cancer risk scientifically defensible?

The combination of U.S. epidemiologic studies of non-smoking women married to smokers provides an appropriate and sound basis for estimating the relative risk of lung cancer associated with ETS among American women who have never smoked cigarettes. The procedures used to estimate the numbers of lung cancer deaths due to ETS among female nonsmokers in the United States are based on a series of reasonable assumptions, and yield a point estimate that is scientifically defensible.

b) Is the approach used to extrapolate lung cancer risk from female never-smokers to male never-smokers and former smokers of both sexes scientifically defensible?

The use of data among non-smoking women to estimate lung cancer deaths (LCDs) due to ETS among non-smoking men offers the advantage of the much greater stability of the estimated effect of ETS among non-smoking women. The epidemiologic studies in the United States have included over 1,000 non-smoking women with lung cancer, but the numbers of non-smoking male cases studied are nearly an order of magnitude smaller, and probably too few to provide an adequate basis for national projections of ETS-related LCDs. Information to make direct estimates of ETS effects among former smokers is even more limited and should take into account their residual risk. Thus, although alternative approaches also might have merit, the approach of extrapolating lung cancer mortality rates among women to men, which was used in the draft document, is scientifically defensible. However, the uncertainties should be further acknowledged. On the other hand, we advise caution in extending the risk assessment to ex-smokers who are known to remain at increased risk of lung cancer well beyond 5 years following cessation of smoking.

c) Are the assumptions used to derive these lung cancer population estimates and the uncertainties involved characterized adequately?

The estimated numbers of lung cancer deaths (LCDs) due to ETS in the United States are based upon several assumptions. For never-smoking women, the

numbers rely on estimates of the relative risk of lung cancer among non-smoking women married to smokers vs. nonsmokers, the effect of potential misclassification of ETS exposure, the relative increase above background in ETS exposure among non-smoking women married to smokers, the proportions of women in various marital/ETS/smoking exposure categories, and the relative risk of lung cancer among female active smokers. Assumptions associated with procedures to derive these estimates are provided, but the draft document does not adequately convey the extent of uncertainty in the resulting estimated numbers of ETS-induced LCDs among never-smoking women. Uncertainties for the estimates among never-smoking males or former smokers are even greater. While the overall point estimate of approximately 3,000 total LCDs due to ETS exposure annually in the United States is based on reasonable assumptions, the citation of a range of 2,500 to 3,300 ETS-related LCDs, based on varying only one of the parameters involved in the estimation, is misleading and implies a greater degree of precision in the estimation than is warranted. The document would be strengthened by additional acknowledgement and characterization of these uncertainties.

d) Is the degree of confidence in these estimates as stated appropriately characterized?

The confidence in these estimates, represented by the range of 2,500 to 3,300 deaths due to ETS, understates the uncertainties associated with each of the assumptions that went into the risk assessment. It indicates a much higher degree of precision than the 90% confidence interval surrounding the summary relative risk for spousal smoking in the U.S. of 1.19. There are other assumptions used in the risk assessment that increase the uncertainty.

### 3.4 Questions Concerning Noncancer Respiratory Disorders - Hazard Identification (Chapter 7; Sections 8.1 and 8.2)

a) Have the biological plausibility arguments been adequately presented?

Biological plausibility has been adequately presented, except for the importance of bronchial responsiveness, especially in relation to lung function growth and decline.

b) Have the most important confounders been properly addressed?

Most of them have. Low birth weight is a confounder that is not adequately considered by many studies. Also, ETS exposure in childhood and adolescence should be included in assessing the effects of ETS on lung function in adults.

c) Has the weight of evidence been properly characterized? Are the conclusions scientifically defensible?

Yes. The weight of evidence has been properly characterized for most sections in Chapter 7, but the evidence for adult pulmonary function does not take into account the potential confounders of childhood respiratory diseases or exposures to parental smoking. The weight of evidence for asthma and sudden infant death syndrome (SIDS) is properly characterized, concluding causality for increased episodes and exacerbation of symptoms in asthmatics, but insufficient evidence for causality for asthma induction or SIDS.

d) Is the evidence with respect to maternal smoking and sudden infant death syndrome properly characterized? Should this evidence be included in this report?

The evidence is appropriately characterized in terms of the strong association and the suggestion that it is impossible, given the existing data, to determine whether this is an *in utero* effect or an effect of environmental smoke exposure.

## 3.5 Questions Concerning Noncancer Respiratory Disorders - Population Impact (Chapter 8)

a) Is the presented population impact of ETS on lower respiratory infections and asthma in children scientifically defensible?

Yes. The issues related to asthma are clearly discussed based on current knowledge. The focus should be on the exacerbation of asthmatic attacks because the etiology of the disease is difficult to define. The issue of childhood respiratory illnesses carries significant weight in the conclusions. It could be expanded, especially for population impact above age 18 months. Potential impact of both asthma and respiratory illnesses on adult lung function and disease could be explored further. The presentation of both a threshold and a non-threshold analysis is balanced, and the levels ascribed are consistent.

b) Are the assumptions, uncertainties, and degree of confidence in the ranges of population impact estimates adequately characterized?

Yes, there is a complete description of the assumptions and uncertainties in the data set. This is a enormous improvement from the first draft of this document, and provides a solid scientifically defensible base upon which to form the conclusions drawn by the document.

# 4. COMMENTS ON THE DRAFT DOCUMENT

This second draft as a whole, is a very substantially improved document and, in general, does a good job of presenting the scientific evidence that supports the judgment that exposure to ETS causes lung cancer and other adverse respiratory health effects. It presents the data and relevant analysis in greater detail than is available in any other single source. The findings in general are well substantiated. The changes made from the first draft to the current draft were carefully thought out and generally appropriate. Also, the authors have done a commendable job in addressing the points raised by the Committee in its review of the first draft. This document will be an invaluable source of information for health professionals and policy makers for years to come.

In preparing the final draft, the Committee recommends that EPA consider a change in organization that we believe would better clarify the nature of the report and its findings. We suggest that Chapters 4, 5 and 6 cover the health effects of ETS on adults, and Chapters 7 and 8 cover the health effects of children rather than having Chapters 4-6 devoted to cancer and Chapters 7 and 8 devoted to other disorders.

## 4.1 Chapter 1 - Summary and Conclusions

The summary and conclusions of the report are clearly described with a brief and appropriate discussion of substantiating evidence. Both the strengths and limitations of the data on which conclusions are based are described. The addition of comments on the relative strengths of the conclusions is also helpful. This chapter will be very useful to the reader who does not have time or the expertise to read the entire document.

A problem with this chapter is that although the findings and conclusions are accurately reported from the document, summary comments and conclusion comments are not clearly separated. The authors may wish to examine summary and conclusions chapters from Surgeon General's reports (DHHS, 1984; 1986) to give them an idea how better to organize this material. Clearly these two should be separated. It would also be helpful to have each summary statement stand alone, be in paragraph form, or be highlighted. In addition, it would also be

helpful if some clearly stated overall objective for the document and specific objectives for each chapter were outlined.

Because of the importance of this Chapter, the conclusions should be clearly highlighted, or a new chapter on Conclusions and Recommendations should be added. At a minimum, we recommend that a new section: **1.3 Conclusions** be added in which the conclusions reached as a result of analyses of findings are summarized.

### 4.2 Chapter 2 - Introduction

This chapter does provide a brief statement of the problem of health risks related to tobacco use. This introductory chapter should clearly establish why ETS is an important problem. The terms "passive smoking," "ETS," and "*in utero* vs. post-natal exposure" need to be more clearly defined. Specifically, it is important to distinguish between passive smoking and ETS. Chapter 2 suffers from excessive use of epidemiologic statistical and risk assessment jargon. It is critical for the general understanding and acceptance of this EPA report that clear language be presented in these chapters to make complex scientific issues accessible and understandable to a lay audience.

### 4.3 Chapter 3 - Estimation of Environmental Tobacco Smoke Exposure

This chapter does a good job of covering the included material. However, there are some important points related to the estimation of exposure to ETS that are not included in the review. These points are important because they affect the interpretation of the exposure and risk estimates.

The introduction to the chapter correctly points out the various factors that can affect the composition of ETS including the variability of emission rates, frequency of smoking, types of products combusted, other sources of the measured components, ventilation rates and effects due to chemistry and deposition losses. However, the review then treats ETS as a material having constant composition with little regard to some of these factors. Three points with respect to the chemical composition of ETS in indoor environments seem especially important.

### 4.3.1 The composition of toxic compounds in ETS

The review should point to the expectation that the toxic potential of a unit mass of ETS is expected to be greater than that of MS. This discussion might also include some comments on the known changes in the chemical composition of ETS as it ages and the unknown impact these changes have on toxicology.

### 4.3.2 The rate of removal of nicotine in indoor environments

Nicotine has been the component of choice as a tracer of ETS in many studies of environmental tobacco smoke because of its uniqueness to ETS and ease of measurement. However, it has also been shown by several investigators that nicotine is the component of ETS that is most rapidly removed in indoor environments. The end result of its removal will be the underestimation of exposure to most other components of ETS when the estimate is based on the concentration of nicotine present in an indoor environment, with the underestimation becoming more severe as the exposure approaches zero. Underestimation will have the same effect as random misclassification, driving the data towards the null hypothesis. This effect should not be ignored.

### 4.3.3 The relative amounts of ETS and non-ETS particles in indoor environments

The text frequently emphasizes the average excess of ETS particulate matter seen in indoor environments where smoking is present, but does not put these numbers into proper context. The impression given is that the bulk of particulate matter in typical indoor environments is from ETS, with high concentrations being rarely measured in the absence of smoking. The average contribution, however, is that about half of the fine particulate matter in a typical indoor environment where smoking is present comes from ETS.

## 4.4 Chapter 4 - Hazard Identification I: Lung Cancer in Active Smokers, Long-term Animal Bioassays, and Genotoxic Studies

This chapter provides a concise and adequate summary of relevant but indirect evidence supporting the biological plausibility for a causal association between long-term exposure to ETS and an elevated risk for lung cancer. The clear dose-related association of lung cancer risk with exposure to MS smoke, the

presence of essentially all of the same known carcinogens in both MS and SS smoke, the laryngeal cancers produced by inhaled MS smoke in the Syrian hamster, and the greater carcinogenic potency of SS tar than MS tar in the mouse skin, all are consistent with an elevated risk of lung cancer in nonsmokers chronically exposed to ETS.

## 4.5 Chapter 5 - Hazard Identification II: Interpretation of Epidemiologic Studies on ETS and Lung Cancer

This chapter provides an overview of 31 epidemiologic studies of ETS and lung cancer, an evaluation of these studies, and a meta-analysis. Summary analyses are presented by geographic region and study quality. The chapter ends with an overall evaluation of the evidence and a conclusion that ETS is a Group A human carcinogen. We support the general approach of reviewing the studies, classifying them by quality, and calculating a pooled measure of association. However, a number of specific problems should be addressed.

a) Lack of a general epidemiologic framework: The chapter fails to set out a general framework for evaluating the studies. The introductory portions of the chapter, in addition to considering the issue of statistical significance, should systematically review the types of bias that may affect case-control and cohort studies. The framework could then be used for evaluating the individual studies. The types of relevant bias can be readily listed: selection bias, information bias resulting in either differential or non-differential misclassification, and confounding. Improper control group selection and statistical power are two additional limitations. We suggest an overall discussion of each of these methodological limitations and the potential consequences for interpreting the studies. This approach would lend itself to evaluating the individual studies.

b) Lack of framework for reviewing individual studies: A second concern, failure to develop a systematic framework for reviewing the individual studies, would be satisfactorily addressed by the approach suggested above.

c) Editing: The text needs further editing. In many instances epidemiologic terminology has been used inappropriately. This imprecision of language may lead to unneeded ambiguity.

d) Confounding: A substantial portion of the text is directed at potential bias introduced by confounding. As noted by the authors, confounding variables are themselves risk factors but are also associated with the exposure of interest. We presently know little about causes of lung cancer in persons who have never smoked. Some occupational factors are causally linked to lung cancer in never smokers but other risk factors have not yet been well established. For example, while diet is emphasized as a potential confounder in the chapter, we are still awaiting confirmation that dietary factors are of importance in the high proportion of lung cases occurring in smokers.

## 4.6 Chapter 6 - Population Risk of Lung Cancer from Passive Smoking

Chapter 6 provides estimates of the numbers of lung cancer deaths (LCD) among nonsmokers in the United States attributed to ETS exposure. Estimates are presented first for female nonsmokers, the group with the largest quantity of relevant data on the effects of ETS. The estimated number of LCDs depends upon the estimate, presented and discussed in Chapter 5, of 1.19 for the relative risk of lung cancer among American non-smoking women married to smokers compared to non-smoking women married to nonsmokers, and the relative risk estimate of 1.59 for these same women corrected for background ETS exposure. Based on these two estimates, and estimates of the relative risk of lung cancer among female smokers compared to nonsmokers, the proportions of non-smoking women exposed to spousal ETS, and the proportion of women who are nonsmokers, the report partitions the approximately 38,000 LCDs in American women in 1985 into about 32,000 due to active smoking, 1,500 due to ETS (1,030 due to background ETS and 470 due to spousal ETS), and about 5,000 due to other causes. No confidence limits are placed about the 1,500 ETS-related LCDs to take into account inherent sampling variation. The report then estimates the numbers of LCDs in 1985 attributed to ETS among male nonsmokers. Limited data on relative risks of lung cancer among non-smoking men married to smoking women are available from 11 studies (7 in the United States), with an overall average relative risk of about 1.6 (1.4 for U.S. studies), but the report does not use these estimates to estimate LCDs attributed to ETS among men. Instead it extrapolates from the more stable

estimated lung cancer mortality rates among non-smoking women married to smokers vs. nonsmokers. So doing yields an estimate of 500 LCDs due to ETS among male nonsmokers.

A similar extrapolation technique is used to estimate the number of LCDs in 1985 due to ETS among male and female former smokers, where former smokers are defined as those who quit smoking 5 or more years ago. The estimated number of ETS-related LCDs among these former smokers is 1,060. The grand total of LCDs attributed to ETS is thus 3,060.

Data from the large, multi-center case-control study of lung cancer among non-smoking women by Fontham et al. (1991) are then used in place of the combined U.S. data to produce alternative total estimates of 2,480 and 3,300 ETS--induced LCDs. The two estimates from this case-control study arise from use of two different estimates (one based on means, the other based on medians) of the ratio of ETS exposure in non-smoking women married to smokers vs. nonsmokers.

The use of data only from American studies to estimate LCDs in the United States seems justifiable. Data from other countries bolster the conclusion that ETS exposure can increase risk of lung cancer in humans (i.e., that ETS is a class A carcinogen), but the magnitude of the effect in the United States seems better estimable using the U.S. data alone. The use of data among non-smoking women to estimate LCDs due to ETS among non-smoking men offers the advantage of the much greater stability of the estimated effect of ETS among non-smoking women. The U.S. studies included over 1,000 non-smoking women with lung cancer, but the number of non-smoking male cases studied appears to be nearly an order of magnitude smaller, and probably too few to provide an adequate basis for national projections of ETS-related LCDs. The chapter cites problems in adjustment for misclassification as the rationale for not using the male data, but a stronger case might be made on grounds of limited information among males and the considerably greater precision of the female data. Nevertheless, the text should more fully discuss the claim that misclassification bias may be greater for male than female nonsmokers, and acknowledge the possibility that the number of ETS--related LCDs among male nonsmokers may be less than, in addition to greater than, the estimate of 500.

The decision to not use cigarette-equivalent low-dose interpolation techniques to estimate the numbers of LCDs due to ETS seems appropriate. It is not clear

which one or several of the many carcinogens in cigarette smoke is responsible for the increased risk of lung cancer in active smokers, nor how variation in bodily cotinine concentration relates to variation in lung exposure to these carcinogens. Thus, there would be considerable uncertainty in using cotinine or other biomarker data to translate ETS exposure by nonsmokers into cigarette-equivalent exposures. The biomarker data clearly show that nonsmokers inhale and metabolize components of tobacco smoke, and help establish that exposure to ETS can increase the risk of cancer, but they are less useful in estimating the number of cancers induced by ETS.

The type of risk estimation done in this section is always subject to error because of inadequate knowledge in many of the parameters and the need to make various assumptions about the relationship of these parameters to one another. The estimates obtained in this section appear reasonable and the assumptions are clearly stated. Analytically it would seem difficult to place confidence intervals that can be interpreted in the conventional context of a sample size. Some indication in this regard could be accomplished with a simulation study. The sensitivity analysis serves to convey the high degree of variability in the estimates but considers primarily one variable at a time. The approach used to estimate lung cancer due to ETS in non-smoking women appears reasonable although the parameters used are presently based on untestable assumptions. The extrapolation to males and ex-smokers requires additional assumptions and, thus, is more difficult to defend scientifically. However, the report states the assumptions made to obtain the estimates.

## 4.7 Chapter 7 - Passive Smoking and Respiratory Disorders Other Than Cancer

This chapter is an important component to the report. This chapter is substantially improved from the previous draft. Section 7.2.2 presents evidence that the *in utero* exposure to cigarette smoke via the mother significantly affects neonatal pulmonary function both in animals and humans. While the evidence is fragmentary, the effects are consistent and convincing overall.

Section 7.2.3 indicates that reduced airway size and reduced respiratory flow rates in neonates are associated with an increased of risk of pulmonary infection during infancy, and possibly a predisposition to chronic obstructive lung disease in adulthood. The section provides an important theoretical link between *in utero* or

early life exposure to cigarette smoke and possible abnormal lung function and pulmonary morbidity in later life.

Sections 7.2.4 and 7.2.5. provide evidence that parental smoking, at least heavy smoking, enhances the likelihood of bronchial hyper-responsiveness and other atopic illnesses in children. These findings are even more striking in light of the "healthy smoker effect". Overall, Section 7.2 provides an excellent overview of biological mechanisms that may underlie the ETS-respiratory disease association.

New data reviewed in Section 7.3 support prior conclusions of the Surgeon General's Report (DHHS, 1986) and the National Research Council (NRC, 1986) report that parental smoking is associated with increased risk of respiratory tract infections in infants. The Chen (1989), Chen et al. (1986; 1988) and Woodward et al. (1990) data demonstrating that *in utero* exposure via maternal cigarette smoking is not the sole explanation for the increased risk represent a valuable new observation. Several potential confounders were discussed and convincingly argued not to account for the observed risk of ETS exposure; these included low birth weight. Low birth weight, the risk of which has been reported to be increased by ETS exposure, would be expected to raise the risk of respiratory infection during infancy.

Section 7.5. The recent studies on cough, phlegm or wheezing and ETS are particularly impressive in that so many studies performed in different countries and with very different methodologies have arrived at similar conclusions. Potential confounders are thoroughly discussed. The conclusion that ETS exposure is associated with an increased prevalence of respiratory symptoms in infants and the young is highly reasonable.

Section 7.6. The new studies in this area offer support for the conclusion that ETS exposure aggravates asthma in children. The discussion that it is more likely chronic rather than acute exposure to ETS that increases airway responsiveness, the importance of high levels of exposure (which may vary seasonally), and the socioeconomic influences on exposure are important for our understanding of the nature of the relationship between ETS and asthma, as well as for developing prevention strategies.

Section 7.7. The studies on maternal smoking and risk of sudden infant death syndrome (SIDS) and the Centers for Disease Control (CDC, 1991) Risk

Assessment are remarkably consistent in showing an increased risk, even though patients were studied in different areas in the U.S. and in different countries around the world. The association between maternal smoking and SIDS persists after controlling for a variety of potential confounders, including low birth weight. However, the relative risks of prenatal and postnatal cigarette smoke exposure cannot be distinguished.

Section 7.8. As noted, the data on ETS and pulmonary health in adults are inconsistent from study to study and potentially confounded by exposure to other respiratory irritants that are linked to socioeconomic class and/or to a greater tolerance by ETS-exposed individuals of other noxious airborne chemicals. Not mentioned in the discussion of potential confounders is the issue of childhood exposure that could influence pulmonary function in adulthood. It is likely that children whose parents smoked, even if they did not become smokers themselves, are more likely to marry a smoker compared to children whose parents do not smoke. Also relevant to the issue is the study of Janerich et al. (1990) indicating that a substantial fraction of life-long environmental ETS exposure occurs during childhood and adolescence.

## 4.8 Chapter 8 - Assessment of Increased Risk for Respiratory Illnesses in Children from Environmental Tobacco Smoke

In general, the risk assessments in this chapter are well done, and tend to be on the conservative side. For one thing, there is a tendency toward an underestimation of the risk associated with the use of cotinine as a measure of exposure to ETS. For another, the risk assessment was limited, for LRI's to those under age 18 months, for asthmatic attacks on children and only those exposed at home and requiring some type of urgent care; it did not include the risk associated with bronchial responsiveness nor the risk associated with ETS-induced respiratory effects in childhood which have high probabilities of producing/impacting on adult respiratory problems.

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